**Abstract**

**Purpose**:A retrospective observational case series to describe ocular manifestations in children with congenital insensitivity to pain.

**Methods**: Records of all patients who visited our outpatient clinic with confirmed congenital insensitivity to pain syndrome were reviewed. Collected data included demographic information, medical history, ocular surgeries, genetic analysis, and ophthalmic examination. Retrieved data included visual acuity, cycloplegic refraction, ocular surface findings, corneal sensitivity, tear film production, and fundoscopy.

**Results**: Six patients were included. Three had mutations at the *PRDM12* gene and 3 at the *SCN9A* gene. Mean follow-up time was 56 months and 130 months, respectively. Corneal opacities were found in 5/6 eyes and 2/6 eyes (2 different patients), respectively. All eyes in the first group had diffuse and dense superficial punctate keratopathies (SPK), whereas sparse and diffuse SPK were found in 4/6 eyes with no SPK in both eyes of 1 patient in the second group. Schirmer was normal in the first group but reduced among all eyes of the second group. Corneal reflex was absent in all patients of the first group, versus positive in both eyes of 2/3 patients from group 2. Best corrected visual acuity (BCVA) was 20/30 in 2 eyes of 1 patient and ≤20/40 in the rest of the first group; among group 2, it was 20/30, except 1 eye of 2 patients had BCVAs of 20/80 and 20/200.

**Conclusion:** Patients with *PRDM12* congenital insensitivity to pain have a poorer prognosis, with severe corneal involvement and lower BCVA, compared with patients with an *SCN9A* mutation.

**Introduction**

Congenital insensitivity to pain is part of a group of extremely rare autosomal recessive neuropathies characterized by the inability to perceive noxious stimuli as pain and heat. Patients are predisposed to self-inflicted injuries and prone to bone fractures and burns that may cause permanent and devastating orthopedic disabilities: intellectual ability and sweat function are preserved.1

Several genetic mutations have been found to correlate with congenital insensitivity to pain. Among them is a missense mutation in the voltage-gated sodium channel type IX α subunit (SCN9A), phenotypically characterized with insensitivity to pain and anosmia while other sensorial modalities remain intact.2

Another mutation that causes congenital insensitivity to pain affects the epigenetic regulator PR domain zinc finger protein 12 (*PRDM12*), interrupting the development of the Aδ and C nociceptive sensory neurons.3

The ocular manifestations of congenital insensitivity to pain include dry eye syndrome, superficial punctate keratopathies (SPKs), corneal opacities, neurotrophic keratopathy, and corneal ulcers.4 *PRDM12* mutation is correlated with reduced lacrimation, corneal abrasions, and reduced or absent corneal reflex, causing keratitis and corneal scarring.3,5 Current literature regarding ocular manifestations in patients with *SCN9A* is inconclusive.

The aim of this study is to describe ocular findings and compare the natural history of the disease in these two groups of patients**.**

**Methods**

This is a retrospective case series of all patients with confirmed diagnosis of congenital insensitivity to pain who visited XXX, between 2009 and 2018. The research was approved by XXX Institutional Review Board and Ethics Committee and fully adhered to the tenets of the Declaration of Helsinki.

All patients were genetically diagnosed at XXX using real-time polymerase chain reaction. They were followed by an ophthalmologist and a pediatrician at XXX. Demographic data and medical histories were obtained from computerized medical records. Ophthalmic data collected included visual acuity (VA), cycloplegic refraction, presence of corneal opacities, SPKs, corneal sensitivity, tear breakup time (TBUT), Schirmer test, and posterior segment findings. Data from ancillary exams (e.g. corneal tomography, anterior segment photos) were included if performed.

Visual acuity was evaluated by Snellen chart. SPKs were measured according to the SPK grading method by Miyata et al.,6 in which the area and density of the lesions were used as parameters to quantify SPKs, where A represents the area of the lesion ranging from A0 – no staining to A3- area occupies more than two thirds of the cornea, and D represents the density ranging from D0- no punctate staining to D3- high density and lesions overlap. Corneal sensitivity was assessed by cotton thread. Telling the patient to fixate on a target, it was applied on the cornea from the lateral side of the eye. If a blink reflex was elicited it was recorded as positive corneal reflex. Tear production was evaluated by Schirmer test after instillation of oxybuprocaine hydrochloride 0.4% for local anesthesia. Schirmer strips (TearFlo®) were inserted into the lower fornix without touching the cornea. The length of wetting in millimeters was recorded after 5 minutes.

Corneal opacity was assessed by three parameters: location (central, eccentric, or peripheral), diameter (less than 2 mm, between 2 and 4 mm, or more than 4 mm), and depth (subepithelial, stromal-superficial, or deep). Active corneal ulcer was defined as a corneal infiltrate with epithelial defect and described by location, diameter, and depth.

**Results**

Demographic data and results are summarized in Table 1. Six patients genetically diagnosed with congenital insensitivity to pain were divided into two groups (A and B) of three patients: Group A had PRDM12 gene mutations and Group B had SCN9Agene mutations. Group A consisted of two first-degree siblings (sister, aged 11 years, and brother, 3 years; patients CIP1 and CIP2), offspring from a consanguineous marriage, and a third unrelated patient (patient CIP3; 6 years old). Group B contained three sisters (24, 16, and 13 years old; patients CIP4, CIP5, CIP6) with the same father but two different mothers.

Follow up time was 23–94 months and 121–143 months for groups A and B, respectively.

All patients in group A versus two in group B (CIP4 and CIP6) presented to the outpatient clinic or ophthalmic emergency room with corneal ulcer by the first year of life: they were hospitalized and treated aggressively with topical and sub-conjunctival fortified antibiotics and by lateral tarsorrhaphy (LT). CIP5 presented at 6 years of age with dry eye complaints and was followed up because of dry-eye syndrome.

In group A, CIP2 had repeated LT and amniotic membrane (AM) transplant due to non-healing corneal ulcers: six LT, five AM in the right eye and seven LT, eight AM in the left eye. He also required two corneal-covering graft transplantations due to descemetocele on his left eye.

The majority of patients had signs of dry eye syndrome with variable severity. In group B, two patients (CIP5 and CIP6) had short TBUT and abnormal Schirmer test results. Moderate dry eye syndrome with localized and dense SPK was observed in CIP4 and CIP6, whereas no SPK was observed in CIP5. All patients required constant eye lubrication. CIP1 and CIP2, who are siblings, underwent therapeutic punctal occlusion.

Corneal reflex was negative (four of six eyes) or not tested (two of six eyes) in group A. A positive corneal reflex was present in CIP4 and CIP6 (four of six eyes) and negative (two of six eyes) in CIP5 in group B.

Corneal opacities were observed in five of six eyes in group A versus two of six eyes in group B.

In group A, visual acuity at the last follow-up visit was 20/30 in both eyes for CIP1; CIP2 had light perception in his right eye and visual acuity could not be determined in the left. CIP3 had a visual acuity of 20/200 in his right eye and 20/40 in the left. In group B, CIP4 and CIP6 had developed amblyopia: visual acuity at the last visit was 20/200 and 20/80 in their amblyopic eyes, respectively, versus 20/30 in the non-amblyopic eye. Both had corneal opacities and astigmatism in the amblyopic eye (Figure 2). CIP5 had a visual acuity of 20/30 in both eyes at the last follow-up visit, with bilateral clear corneas and no signs of dry-eye syndrome.

**Discussion**

Congenital insensitivity to pain is a rare disorder and little is known about its ocular manifestations. Patients with different genetic mutations have not been compared yet. In this study we compared ocular manifestations in patients with *PRDM12* mutations with those in patients with *SCN9A* mutations.

We found that patients with *PRDM12* mutations (group A) tended to have a poorer ocular prognosis and visual acuity than patients with *SCN9A* mutations (group B). All in group A had absent corneal reflex, versus one patient in group B.

Corneal opacities and SPK grade were higher in all patients in group A: two patients in group B had milder SPK grade and one had no SPK. Tear production was decreased among all patients in group B, but normal in the only patient for which it was measured in group A.

Refractory non-healing corneal ulcers that required surgery were more frequent and tended to be more severe and difficult to treat in group A than group B.

Similar results regarding corneal reflex and corneal opacities have been reported previously in patients with *PRDM12* mutations. In one study of affected individuals from 11 families, absent corneal reflex led to progressive corneal scarring in many cases. They also tended to have reduced tear function.3 In another study of five individuals (23–57 years of age), all with decreased tear production and no corneal reflex, two had no useful vision in one eye.5

Ocular findings vary among patients with *SCN9A* mutation. The corneal reflex was intact in three studied patients (31, 34, and 44 years old),7 whereas in a previous study of four patients, three of whom are also included here, all had decreased or absent corneal reflex but normal lacrimal production.2 One reported case had absent corneal reflex and developed bilateral sterile corneal ulcers that were attributed to neurotrophic keratopathy.8

We think the that these findings are the result of different phenotypic expression that varies due to variable penetrance of the mutation.

In our study, all but one case of corneal ulcer occurred before the age of 2 years. These could have been prevented if parents were aware of such complications and of ways to prevent them.

In conclusion, we note that patients with *PRDM12* mutations have a more serious ocular involvement than patients with *SCN9A* mutations, but both can develop corneal ulcers at an early age. Outcomes tend to be better among patients with *SCN9A* mutation, which is probably because of some degree of preserved corneal sensitivity compared with patients with *PRDM12* mutation.

Ocular manifestations in both groups may represent variable degrees of neurotrophic keratopathy and the different manifestations are due to a variable degree of corneal hypoesthesia or anesthesia. Our case series is highly limited due to the small number of patients, lack of control subjects, and by its retrospective nature. More studies are required in order to determine the genotype phenotype correlation in these disorders.

**References**

1. Schon K, Parker A, WoodsCG. Congenital Insensitivity to Pain Overview. 2018 Feb 8 [Updated 2020 Jun 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK481553/.

2. Cox JJ, Sheynin J, Shorer Z, et al. Congenital insensitivity to pain: Novel SCN9A missense and in-frame deletion mutations. Hum Mutat 2010;31(9):E1670-86. doi:10.1002/humu.21325.

3. Chen YC, Auer-Grumbach M, Matsukawa S, et al. Transcriptional regulator PRDM12 is essential for human pain perception. Nat Genet 2015;47(7):803-8. doi:10.1038/ng.3308.

4. Mimura T, Amano S, Fukuoka S, et al. *In vivo* confocal microscopy of hereditary sensory and autonomic neuropathy. Curr Eye Res 2008;33:940-5. doi:10.1080/02713680802450992.

5. Zhang S, Sharif SM, Chen Y, et al. Clinical features for diagnosis and management of patients with PRDM12 congenital insensitivity to pain. J Med Genet 2016;53:533-5. doi:10.1136/jmedgenet-2015-103646.

6. Miyata K, Amano S, Sawa M, Nishida T. A novel grading method for superficial punctate keratopathy magnitude and its correlation with corneal epithelial permeability. Arch Ophthalmol 2003;121(11):1537-9. doi:10.1001/archopht.121.11.1537.

7. McDermott LA, Weir GA, Themistocleous AC, et al. Defining the functional role of NaV 1.7 in human nociception. Neuron 2019;101(5):905-19.e8. doi:10.1016/j.neuron.2019.01.047.

8. Jarade EF, El-Sheikh HF, Tabbara KF. Indolent corneal ulcers in a patient with congenital insensitivity to pain with anhidrosis: A case report and literature review. Eur J Ophthalmol 2002;12(1):60-5. doi:10.1177/112067210201200112.

9. Shaheen BS, Bakir M, Jain S. Corneal nerves in health and disease. Surv Ophthalmol 2014;59(3):263-85. doi:10.1016/j.survophthal.2013.09.002.

**Figure legends**

**FIG 1.** Pedigree of family with congenital insensitivity to pain. Filled symbols indicate affected individuals. Small round filled symbols indicate abortions. Squares indicate males and circles females. Diagonal line across a symbol = deceased individual.

**FIG 2.** Right eye of patient CIP5 showing central corneal opacity. Note the notch in upper and lower eyelids where tarsorrhaphy was made.

**FIG 3.** PENTACAM® tomography, right eyes of patients CIP4 and CIP5 showing high with-the-rule astigmatism.